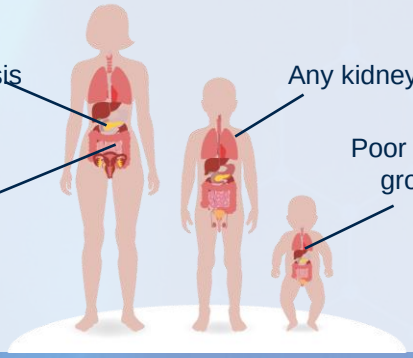
Consider PH1 Early As Disease Progression in PH1 May Lead to Kidney Failure

Click on + symbols throughout to learn more

PH1 severity is variable and the disease presents differently in different age groups[1–4]

It is important to suspect PH1 in individuals with common symptoms, which include:[1,4]



+ Click for more PH1 symptoms

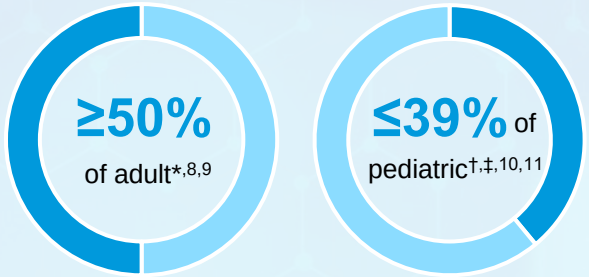
+ Click to explore the **characteristics of kidney stones** indicative of PH1

Primary Hyperoxaluria Type 1 (PH1) is a **rare**, **genetic**, metabolic disorder characterized by the **overproduction of oxalate** by the liver[5,6] +

Diagnostic delay is a key challenge in PH1[7]
The median delay is 5.5 years in adults[8] +

Delayed diagnosis may lead to significant morbidity and mortality. Oxalate accumulation may lead to progressive kidney damage and systemic oxalosis[1,12,13]

% patients with **ESKD at diagnosis**



Overview of the diagnostic recommendations for the identification of PH1[14–16]

+ Click for the PH diagnostic algorithm

This information is being provided for educational purposes only and is not intended to replace the independent medical judgment of any healthcare professional. *Based on a population of 10 patients who were diagnosed with PH1 as adults in a cohort study;[8] †Based on a retrospective review of 18 children with PH1;[10] ‡Based on a retrospective study of 526 adult and pediatric patients with PH1;[11] §For patients, especially children, who are unable to provide a 24-h UOx, consider measuring spot UOx:Cr;[14,15] ¶For use in patients with residual urine output.[16]

+ Click for references and abbreviations

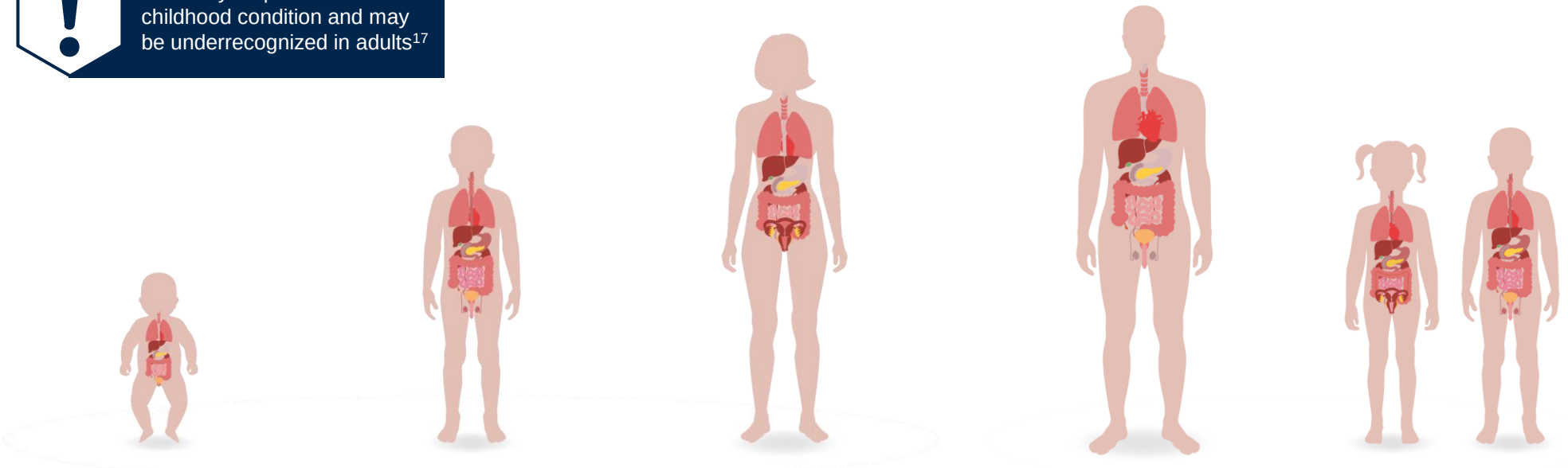
Intended for US HCPs
Scan the QR code to learn more on the RNAi Science website

February 2025 | MED-US-GO1-2400023

Primary Clinical Manifestations of PH1 Can Look Different in Different Populations[1–4]

Relative Incidence (%) and Typical Features of PH1 Phenotypes at Initial Presentation

PH1 may be perceived as a childhood condition and may be underrecognized in adults[17]



Age[1–4]

Infancy (~10%)

- Nephrocalcinosis
- Kidney impairment/failure
- Poor weight gain
- UTI

Childhood (~60%)

- Kidney colic
- Hematuria
- UTI
- Recurrent urolithiasis
- Nephrocalcinosis
- Acute kidney failure

Adulthood (<10%)

- Mild to moderate decline in kidney function
- Acute kidney failure
- Nephrocalcinosis
- Recurrent kidney stones
- CKD

Post-KTx[1]

Disease recurrence (~10%)

- Subsequent increase in serum creatinine
- CaOx crystals on biopsy
- Graft failure

Screening[1]

PH1 family history (<10%)

- Diagnosis in a symptomatic sibling
- Diagnosis in a presymptomatic individual due to family history

These are not all the signs and symptoms of PH1.

Click for references and abbreviations

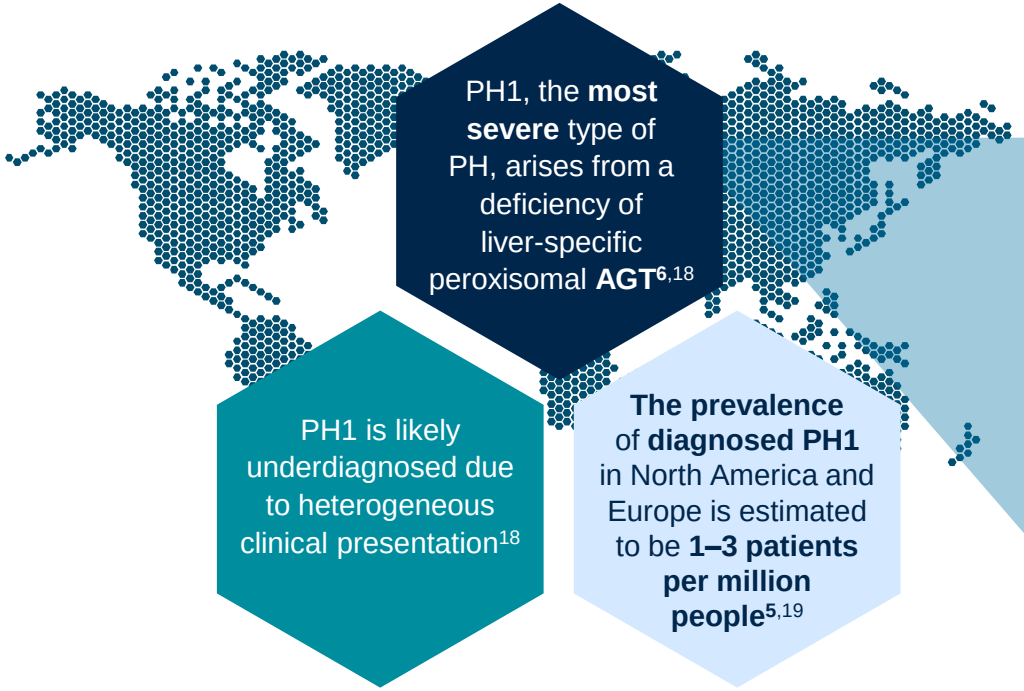
PH1 Is the Most Common and Severe Form of PH Worldwide and Is Caused by *AGXT* Gene Variants[2,18]

PH constitutes a group of rare, metabolic disorders caused by recessive genetic variants[5,6]

PH arises from inherited enzyme deficiencies that lead to the accumulation of oxalate, the end product of glyoxylate metabolism. Each PH type is caused by a different gene variant and enzyme deficiency.[5,6,19]

Causes of PH types[6,18]

- **PH1 (~70% of PH cases):** *AGXT* gene variants
- **PH2:** *GRHPR* gene variants
- **PH3:** *HOGA1* gene variants



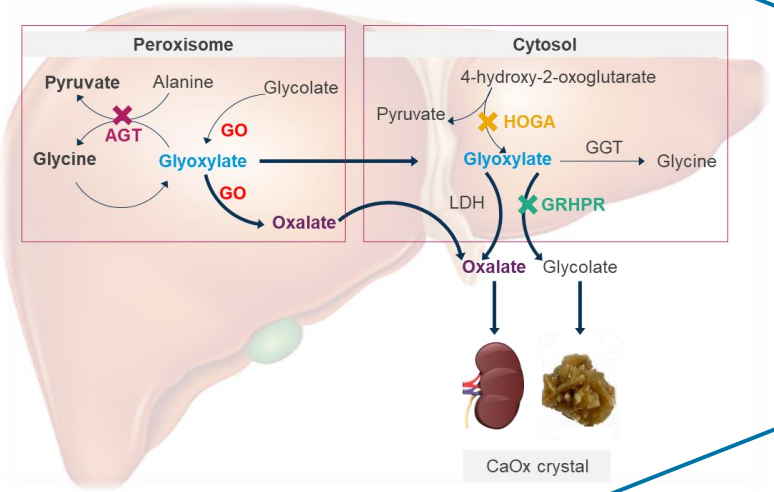
PH1, the **most severe** type of PH, arises from a deficiency of liver-specific peroxisomal **AGT**[6,18]

PH1 is likely underdiagnosed due to heterogeneous clinical presentation[18]

The prevalence of **diagnosed PH1** in North America and Europe is estimated to be **1–3 patients per million people**[5,19]

PH1 pathophysiology and the role of oxalate[5,20]

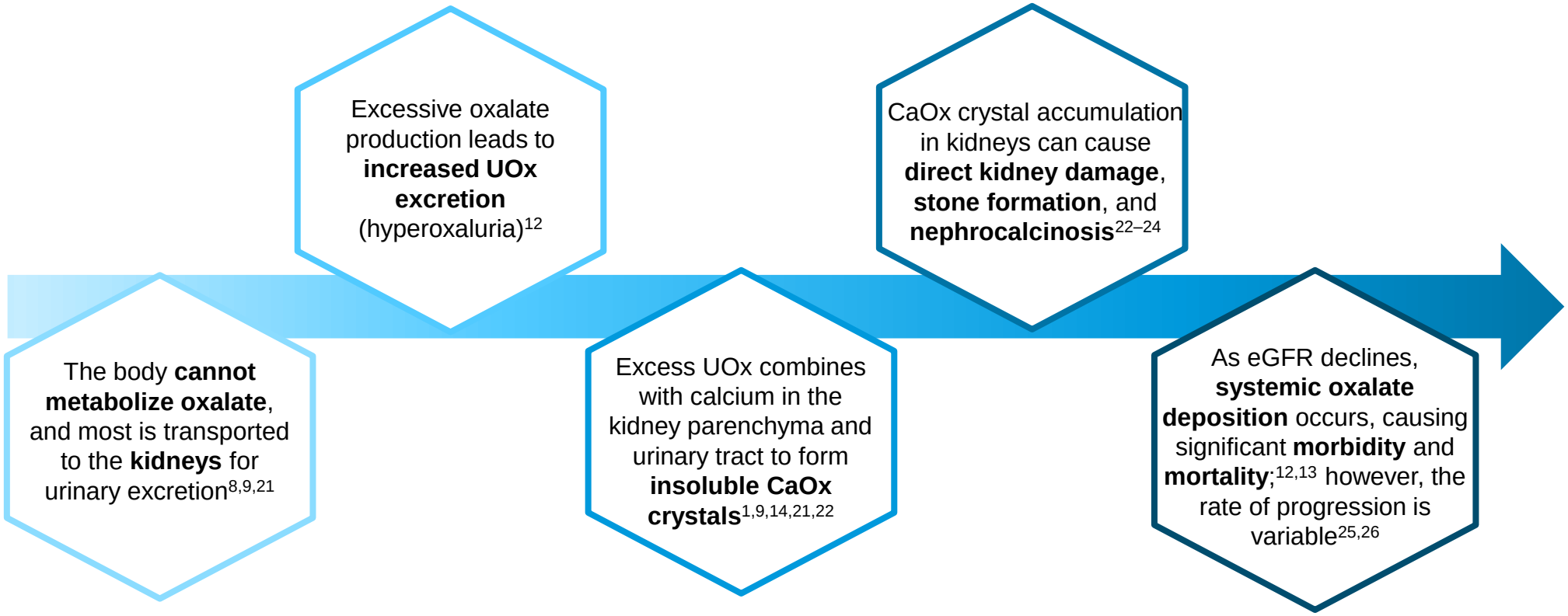
PH1 is caused by a deficiency of liver-specific peroxisomal AGT, leading to oxalate accumulation[6,18]



Click for references and abbreviations

Identify PH1 Early in Diagnostic Workup: Oxalate Overproduction May Lead to ESKD and Systemic Oxalosis[1–3]

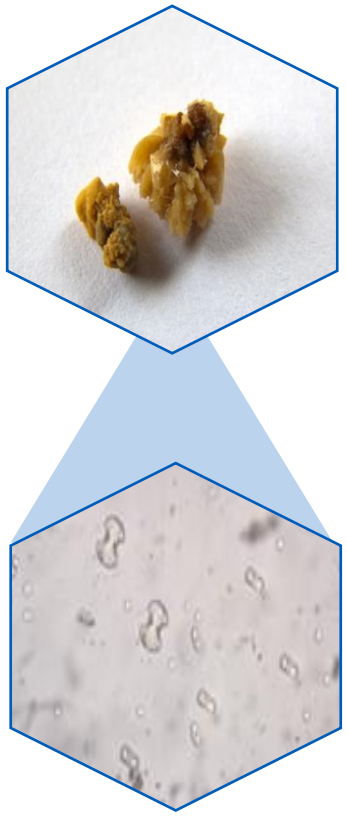
The Role of Oxalate in PH1 Pathophysiology



Diagnostic delay may be avoided by being aware of the signs and symptoms of PH1 and facilitating testing of appropriate patients[9,22]

Click for references and abbreviations

Analyses in Patients With PH1 Have Identified Kidney Stone Characteristics



Magnified image

Kidney Stone Characteristics[16]

- Typically, **calcium oxalate monohydrate** (whewellite) stones
- **Peculiar morphology** reflecting speed of formation
  - White or pale yellow instead of brown
  - Disorganized internal structure
  - Radiating inner structure

Kidney stones are one of the most common symptoms of PH1; however, not all patients with PH1 are stone formers[16,19,27]

Click for references and abbreviations

Diagnostic Algorithm: Published Recommendations for the Diagnosis of Patients with Suspected PH[14–16]

Relatively Preserved Kidney Function

- Nephrocalcinosis[14–16]
- CaOx stones in children or recurrent stones in adults[14–16]
- Family history of PH, childhood or recurrent stones, or unexplained kidney disease[14,15]

↓

UOx testing[14–16]

UOx >0.5–1 mmol/1.73 m^2/24 hours or UOx:Cr ratio >normal for age[14]

Confirmed high UOx on repeat testing[14–16]

↓

Urine metabolites testing[14–16]

(glycolate, L-glycerate, 4-hydroxy-2-oxoglutarate)

Glycolate or glycerate >2×normal[15]

↓

OR

CKD Stage 3 and Beyond or on Dialysis

- Nephrocalcinosis[14–16]
- CaOx stones in children or recurrent stones in adults[14–16]
- CaOx tissue deposits[14,15]

↓

POx and/or UOx* testing[14–16,†]

POx >20 µmol/L[14,15]

UOx >0.5–1 mmol/1.73 m^2/24 hours or UOx:Cr ratio >normal for age[14]

↓

Secondary cause identified?[14,15]

- Malabsorption
- Gastrointestinal disease
- Very high-oxalate, low-calcium diet
- Premature infant

Yes → **Evaluate and treat accordingly[14,15]**

No ↓

Genetic testing[14–16]

Homozygosity or compound heterozygosity for known variants of *AGXT*, *GRHPR*, or *HOGA1*

Yes ↓

- *AGXT* variants → PH1
- *GRHPR* variants → PH2
- *HOGA1* variants → PH3

Figure adapted from Michael M et al. 2024,[14] Edvardsson VO et al. 2013,[15] and Groothoff JW et al. 2023[16]

This information is being provided for educational purposes only. It is not intended to replace the independent medical judgment of any healthcare professional. Note that PH includes three types: PH1, PH2, and PH3. *For use in patients with residual urine output;[16] †As patients on dialysis without PH can have average POx levels between 50 and 60 µmol/L, patients on dialysis with PH may have even higher values.[16]

Click for references and abbreviations

UOx Testing is Recommended in Patients with Relatively Preserved Kidney Function as a Key Measure of PH1 Diagnosis[14]

UOx

POx

Measuring UOx in Patients with Relatively Preserved Kidney Function

Collect **24-hour urine sample**[14]

Repeat test to confirm UOx elevation[14]

Suggestive of PH: UOx levels above 0.5–1 mmol/1.73 m^2 per day*,[14,16,28]

*Utilize lab with experience measuring plasma and urine oxalate.[16]

Click for references and abbreviations

UOx Testing is Recommended in Patients with Relatively Preserved Kidney Function as a Key Measure of PH1 Diagnosis[14]

UOx

POx

Measuring UOx in Patients with Relatively Preserved Kidney Function

Age Considerations[14]

- The results of 24-hour UOx should be corrected to 1.73 m^2 BSA
- A random UOx:Cr can be used if there are challenges with timed urine collection
- **Suggestive of PH:** Random UOx:Cr higher than normal*

Differential Diagnosis[14,16]

- Exclusion of secondary causes of hyperoxaluria is required before genetic investigations

*Random UOx:Cr vary significantly by age. Consult pediatric reference tables for interpretation.[14]

Click for references and abbreviations

In Patients with CKD Stage 3 and Beyond or on Dialysis, POx is Recommended as a Main Measure of PH1 Diagnosis*,[14,16]

UOx

POx

Practical Considerations for Measuring POx

Blood sample **must be placed on ice** and sent to the laboratory **immediately** as plasma has to be separated rapidly from cells[16,29]

- Variations in POx levels due to **differences in assays and reference laboratories can cause confounding when interpreting results**[14] therefore utilization of the same laboratory is recommended for POx tests[30]

Measuring POx in Patients with CKD Stage 3 and Beyond[14,16]

- POx should be corrected for eGFR, as POx increases with decreasing eGFR[16]

Suggestive of PH: POx levels above 20 µmol/L[14]

*UOx can be considered for use in patients with residual urine output.[16]

Click for references and abbreviations

In Patients with CKD Stage 3 and Beyond or on Dialysis, POx is Recommended as a Main Measure of PH1 Diagnosis*,[14,16]

UOx

POx

Measuring POx in Patients on Dialysis[14,16]

As patients on dialysis **without PH can** have average POx levels between 50 and 60 micromols/L, patients on dialysis with PH may have even **higher values**

Suggestive of PH: POx levels >50–60 µmol/L†

This information is being provided for educational purposes only. It is not intended to replace the independent medical judgment of any healthcare professional.

*UOx can be considered for use in patients with residual urine output;[16] †Utilize lab with experience measuring plasma and urine oxalate.[16]

Click for references and abbreviations

Genetic Testing can Help Confirm the Diagnosis of PH1*

A presumptive diagnosis of PH by UOx or POx can be confirmed by molecular testing of *AGXT* gene for PH1[14]

Genetic confirmation of PH1 is important because:

- Elevated biochemical parameters may be due to various etiologies[16]
- It has a direct impact on clinical management[31]
- It can have implications for family planning[16,31]

Ideally, after biochemical testing and clinical assessment leads to suspicion of PH, **genetic testing** should be performed as **early as possible**[16]

PH1 is an autosomal recessive disease[14]

It is recommended to offer genetic counseling to **patients with PH1 and their families**[14,16]

- Screening of **all at-risk relatives** (symptomatic or not)[14,16]
- Also important for:[14,16]
  - Carrier testing
  - Prenatal testing

This information is being provided for educational purposes only. It is not intended to replace the independent medical judgment of any healthcare professional.

*After excluding secondary causes of PH1.[16]

Click for references and abbreviations

Abbreviations and References

AGT, alanine-glyoxylate transaminase; AGXT, alanine-glyoxylate aminotransferase; BSA, body surface area; CaOx, calcium oxalate; CKD, chronic kidney disease; Cr, creatinine; ESKD, end-stage kidney disease; eGFR, estimated glomerular filtration rate; GO, glycolate oxidase; HCP, healthcare professional; KTx, kidney transplant; PH, primary hyperoxaluria; PH1, PH type 1; PH2, PH type 2; PH3, PH type 3; POx, plasma oxalate; UOx, urinary oxalate; UOx:Cr, urinary oxalate to creatinine ratio; UTI, urinary tract infection.

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